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<b>(54) Title:</b> SKIN TREATMENT FORMULATION AND USES THEREOF  <b>(57) Abstract</b>  The skin treatment preparation comprises, in combination: collagen; elastin; an optional vasodilatory substance; at least one acid chosen from deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), or a salt thereof; a vehicle and/or an excipient.		

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"Skin treatment formulation and uses thereof"

DESCRIPTION

Technical field

The present invention relates to a compound for  
5 the treatment of skin pathologies and unaesthetic  
conditions and optionally of pathologies of the skin and  
related tissues. More particularly, the invention relates  
to a product for the treatment of:

1. skin atrophy striae,
- 10 2 skin wrinkles,
3. ageing of the skin,
4. hair loss and alopecia,
5. chapping of the skin,
6. slow cicatrization,
- 15 7. skin atrophy pathologies of various types,
8. scars.

The invention also relates to the uses of the  
said compound.

Background art

20 Skin atrophy and the phenomena associated  
therewith are mainly due to a deficiency in the two  
proteins of the skin, collagen and elastin, the first  
being responsible for nourishing and revitalizing the  
skin tissues while the second has the function of making  
25 the skin tissues elastic.

More generally, three main aspects which  
characterize skin atrophy may be identified:

- a) deficiency or lack of collagen in the skin;
- b) deficiency of lack of elastin in the skin;
- 30 c) lack of or reduction in vascularization.

There are two approaches to treating skin  
atrophy, involving the integration of the two proteins  
into the skin: supplying the two proteins directly and  
supplying the corresponding amino acids, which allow the  
body to reproduce these proteins by itself, that is to  
35 say to metabolize them. Treatment of skin pathologies by  
integration of collagen and elastin proteins has already  
been attempted, in particular by topical application of

ointments containing the said proteins.

Direct administration of the proteins is theoretically the fastest route, since the body is supplied directly with the proteins it lacks rather than the components (amino acids) via which it metabolizes these proteins.

However, the treatment methods and the relevant compounds used hitherto have not given satisfactory results. The reason for this is that the mainly topical administration of the two proteins affords a transient and therefore unsatisfactory result, or even shows no results at all owing to the fact that the protein is not absorbed on account of the skin barrier.

#### Disclosure of the invention

The subject of the present invention is a product for the treatment of skin pathologies and unaesthetic conditions and optionally of pathologies of the skin, based on elastin and collagen, which product makes it possible to obtain better and especially longer lasting results.

Basically, the product of the invention contains a combination of at least the following components:

- 1) collagen,
  - 2) elastin,
  - 3) preferably at least one local vasodilatory substance
  - 4) at least one acid chosen from deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), or a salt thereof,
- in combination with a suitable vehicle which may also consist of a physiologically acceptable solution, depending on the type of administration for which the formulation is intended.

The combination of these four components makes it possible to obtain results which are markedly superior to those which can be obtained with the products currently available, by virtue of the simultaneous presence not only of the two fundamental proteins but also of an optional vasodilator and at least one of the

RNA or DNA acids, which play a fundamental role in the treatment, as will be clarified later.

In certain cases, a reduction in vascularization accompanies the unaesthetic skin conditions mentioned. In these cases, administration of the optional local vasodilator together with the collagen and elastin, makes it possible to re-establish peripheral blood circulation in the zone treated, thereby giving rise to localized vasodilation and thus allowing the two proteins to reach the treated zones. Moreover, the temporary vasodilation produced by the vasodilatory substance helps vascularization in the tissues and facilitates the provision of nutrients by the blood.

If there is poor vascularization of the tissues treated, despite the administration of a vasodilator together with the proteins, some of the proteins administered may not be bound to the tissues concerned but will be absorbed by the body. The simultaneous provision of at least one of the ribonucleic and deoxyribonucleic acids, or of a salt thereof, allows the tissues treated autonomously to reproduce the two types of protein administered. The reason for this is that DNA helps the tissues receiving it to manufacture proteins with characteristics similar to the proteins administered, while RNA serves to create a memory, in the tissues receiving it, for the two proteins supplied in order to allow the tissues themselves to reproduce these proteins.

The use of one of the two acids RNA or DNA therefore makes it possible to accelerate the healing process by stimulating the autonomous production of collagen and elastin by the skin tissues being treated.

The two acids (or their salts) are preferably used in combination, but appreciable results may also be obtained with only one of the two acids or the respective salt.

According to an improved feature of the invention, the compound may comprise, besides the four

main components referred to above, ~~one or more secondary components chosen from one or more of the following groups:~~

- ~~- amino acids;~~
- 5 - enzymes and coenzymes;
- Vitamin C
- keratin (restricted to treatment of the scalp).

Among the amino acids which may be used in the product according to the invention, mention may be made  
10 of the following: glycine, proline, hydroxyproline, lysine, tyrosine, isodesmosine. Among the useful enzymes for the use according to the invention are the following: pepsin, pyridoxine (Vitamin B6 coenzyme), biotin or Vitamin H (Vitamin B6 coenzyme).

15 The amino acids added to the formulation metabolize the proteins, that is to say they are involved in the formation of collagen and elastin. The enzymes and coenzymes are catalysts of the process of protein metabolism, that is to say they increase the rate of  
20 biochemical reaction of the amino acids to proteins. Their presence in combination with amino acids therefore accelerates the metabolization of protein.

The presence of antioxidant, represented by Vitamin C, makes it possible to reduce the oxygen  
25 requirement of the cells.

Keratin, the use of which is limited to formulations for treating the scalp, constitutes specific nourishment for promoting the regrowth and strengthening of the hair.

### 30 Detailed description of preferred embodiments

The composition of the product varies depending on the mode of administration, in particular as regards the vehicles and the excipients. As regards the four  
35 fundamental components (or five in the case of the use of both DNA and RNA), they may be used in the following amounts, expressed in parts by weight, including in the absence of other components:

Hydrolysed collagen:

3-10 parts

	Hydrolysed elastin:	1-4 parts
	Procaine hydrochloride (vasodilator)	1-3 parts
	Sodium deoxyribonucleate (DNA)	3-10 parts
	Sodium ribonucleate (RNA)	3-10 parts
5	Excipients and vehicles	qs

The sodium deoxyribonucleate and ribonucleate can be used independently of or in combination with each other.

Particularly good results are obtained with compositions varying within the following ranges, again expressed in parts by weight:

	Hydrolysed collagen:	5-9 parts
	Hydrolysed elastin:	2-4 parts
	Procaine hydrochloride (vasodilator)	1.5-2.5 parts
15	Sodium deoxyribonucleate (DNA)	4-8 parts
	Sodium ribonucleate (RNA)	4-8 parts

in the presence of appropriate vehicles and/or excipients. The latter may vary depending on the applications and the form of administration. For administration by subcutaneous or intradermal injection or infiltration, the components mentioned above are prepared in a physiological solution, which in this case represents the vehicle. Typically, the parts by weight shown above are combined with 1000 parts by weight of physiological solution. Appropriate excipients and vehicles are used for topical administration, and a few examples of these will be given in the following text together with respective amounts, with respect to a few particularly effective formulations.

As mentioned above, faster results may be obtained with the addition of secondary components, such as certain enzymes and amino acids. A formulation to which all the secondary components mentioned above have been added is given below. The composition relates to an amount of 10 ml, equivalent to 10 g in physiological solution:

	Hydrolysed collagen:	30-100 mg
	Hydrolysed elastin:	10-40 mg

	Procaine hydrochloride:	10-30 mg
	Sodium deoxyribonucleate	30-90 mg
	Sodium ribonucleate	30-90 mg
	Glycine	25-75 mg
5	Proline	100-300 mg
	Hydroxyproline	25-75 mg
	Lysine	75-225 mg
	Tyrosine	5-15 mg
	Isodesmosine	20-60 mg
10	Pepsin	375-1125 mg
	Pyridoxine	250-750 mg
	Biotin	25-75 mg
	Vitamin C	250-750 mg
	Hydrolysed keratin (*)	15-45 mg
15	(*) only for treatment of the scalp	
	Physiological solution	qs

The best results were obtained with formulations having compositions encompassed within the following ranges, again relative to 10 g of product:

20	Hydrolysed collagen:	45-85 mg
	Hydrolysed elastin:	15-35 mg
	Procaine hydrochloride:	15-25 mg
	Sodium deoxyribonucleate	40-80 mg
	Sodium ribonucleate	40-80 mg
25	Glycine	35-65 mg
	Proline	140-260 mg
	Hydroxyproline	35-65 mg
	Lysine	100-200 mg
	Tyrosine	7-13 mg
30	Isodesmosine	30-50 mg
	Pepsin	525-975 mg
	Pyridoxine	350-650 mg
	Biotin	35-65 mg
	Vitamin C	350-650 mg
35	Hydrolysed keratin (*)	20-40 mg
	(*) only for treatment of the scalp	
	Physiological solution	qs

The compositions given above remain valid for



topical application as regards the first fifteen components, except that they would be in a different and higher concentration, in view of the increased difficulty of absorption and the increased dispersion. Moreover, the physiological solution would be replaced by a combination of various vehicles and excipients.

Typically, in a cream for the local treatment of atrophy, the following compositions may be used, relative to 10 g of product (where the preferred amounts, again in mg, are shown in parentheses):

	Hydrolysed collagen:	65-200 mg (90-170)
	Hydrolysed elastin:	25-75 mg (30-70)
	Procaine hydrochloride:	20-60 mg (30-50)
	Sodium deoxyribonucleate	60-180 mg (80-160)
15	Sodium ribonucleate	60-180 mg (80-160)
	Glycine	50-150 mg (70-130)
	Proline	200-600 mg (280-520)
	Hydroxyproline	50-150 mg (70-130)
	Lysine	150-450 mg (200-400)
20	Tyrosine	10-30 mg (15-25)
	Isodesmosine	40-120 mg (60-150)
	Pepsin	750-2250 mg (1050-1950)
	Pyridoxine	500-1500 mg (700-1300)
	Biotin	50-150 mg (70-130)
25	Vitamin C	500-1500 mg (700-1300)
	Sodium hydroxide	0-15 mg (2-10)
	Vehicle (hydrogenated polyoxyethylenated castor oil)	100-300 mg (150-230)
	Excipient (acrylic acid polymer)	50-200 mg (80-140)
30	Deionized water	qs 10 grams

The same composition may be employed for a product in ampules for topical use in the treatment of atrophy, in which case the excipient is replaced by water, with the addition of preserving agents. Ampules for the treatment of the scalp may have the same composition as ampules for the treatment of atrophy, with the addition of keratin in an amount of from 60 to 120 mg

per 10 g of product.

In all the compositions, the DNA and the RNA may also be used in the form of potassium deoxyribonucleate and potassium ribonucleate or in  
5 another compatible form.

In the case of a product for topical use, vehicles other than the ones mentioned may also be used. However, hydrogenated polyoxyethylenated castor oil has given particularly advantageous results since it allows  
10 the skin barrier to be crossed efficiently.

In the case of preparations for application by subcutaneous or intradermal injection or infiltration, it is advantageous to provide for the addition of sodium bicarbonate in order to eliminate the burning sensation  
15 caused by the acidity and the presence of the physiological solution.

The application methods vary depending on the type of treatment and on the route of administration. The latter may be carried out topically or by infiltration  
20 via subcutaneous, intra- or mesodermal injection of the compound into the site of the atrophies. The number of applications and the amount of product applied vary according to the area of tissue to be treated and its condition. A few general indications are given below,  
25 which a person skilled in the art will use as a guideline for selecting the most suitable mode of application in each individual case. In the case of treatment by infiltration:

1. Treatment of cutaneous striae: subcutaneous  
30 infiltrations are performed, using a syringe with a microneedle, by inserting the needle parallel to the surface of the stria along its entire length. On inserting the needle, a tunnel is formed which is filled with the solution as the needle is withdrawn.
- 35 2. Treatment of skin wrinkles: intradermal infiltrations are performed, using a syringe with a microneedle, by inserting the needle parallel to the surface of the wrinkle along its entire length. On inserting the needle,

a tunnel is formed which is filled with the solution as the needle is withdrawn.

3. Treatment of skin ageing: mesodermal infiltrations (that is to say infiltrations into the dermis but to a deeper level than intradermal infiltrations) are performed, with a syringe with a microneedle, in order to provide deep and diffuse nourishment for the tissues concerned.

4. Treatment of the scalp and of alopecia: intradermal infiltrations into the scalp (trichomesotherapy) are performed using a syringe with a microneedle.

5. Treatment of skin chapping: intradermal infiltrations are performed into the area concerned using a syringe with a microneedle.

6. Treatment of slow cicatrization: intradermal infiltrations are performed into the area concerned using a syringe with a microneedle.

For all the applications listed above, the number of applications depends on the seriousness of the condition of the tissue treated. In general, the number of applications may range from 5 to 50. The amount of solution administered varies according to the size of the area under treatment. Generally speaking, about 0.1 ml of product per  $\text{cm}^2$  of tissue treated may be applied in the treatment of cutaneous striae.

Cosmetic treatment by means of topical application of the compound is carried out by rubbing the ampule preparation onto the area to be treated or by massaging into the area concerned in the case of cream preparations. Topical use involves application twice daily over a period varying between one and six months, depending on the seriousness of the condition of the skin tissue.

With regard to treatment of the scalp, the administration of 2 ml of preparation per application may be envisaged for treating the entire scalp, while for atrophy and ageing of the skin, 1  $\text{cm}^3$  of cream or 1 ampule containing 1 ml of solution is used per 500  $\text{cm}^2$  of

surface area.

-Preparation of the composition:

An example for the preparation of the following formulation is given hereinafter:

5	NaCl aqueous solution (0.9%):	
	stabilized pig-collagen	30 g/l
	sterilized pig-elastin	10/15 g/l
	glycine	2/4 g/l
	proline	6/10 g/l
10	hydroxyproline	2/4 g/l
	Lysine	5/15 g/l
	Tyrosine	1/3 g/l
	Pepsin	10/30 g/l
	pyroxidine	10/30 g/l
15	DNA	60 g/l
	RNA	60 g/l
	Biotin	3/6 g/l
	Procaine	1/3 g/l

20 Collagen and elastin may be of animal or vegetal origin. A process for obtaining hydrolysed cross-linked collagen and hydrolysed cross-linked elastin is described hereinbelow:

- A. stabilised pig-collagen is mixed in a vacutainer under nitrogen atmosphere at 35/38° for 90 min.;
- 25 B. the product is filtered on a 1-micrometre filter;
- C. the filtered product is subject to centrifugation at 3500 rpm for 10 min.;
- D. the supernatant is eliminated in order to obtain a perfectly clear product;
- 30 E. after centrifugation the corpuscular part is brought to its starting volume again, by replacing the removed supernatant with a 3% glutoraldehyde or cross-linked polyvinylpolyppyrrolidone solution;
- F. the solution thus obtained is mixed for 30 min at 35 35/38°C;
- G. steps C, D and E are repeated;
- H. the solution is made to rest for 12 hours;
- I. thereafter the solution is subject to centrifugation at

3500 rpm for 2 hours;

J. the supernatant is removed.

On the bottom of the container a translucent homogeneous gelatine is collected. The gelatine may be brought at the desired viscosity by addition of a  
5 sterilized 0.9% aqueous solution of NaCl.

The same process can be used to produce cross-linked elastin starting from sterilized pig-elastin.

Hydrolyzed aminoacids, hydrolyzed DNA and RNA  
10 and hydrolyzed biotin as well as procaine hydrochloride are added to the proteins treated as above described in order to obtain the above preparation.

The same process can be used with twice the amount of elastin and collagen (i.e. 60 g/l collagen and 20/30  
15 g/l elastin.

The product thus obtained is sucked in a syringe or other suitable container and the final package sterilized with gamma-irradiation. The whole process is performed in a white chamber (class "100") under laminar flux hood.

20 It should be understood that the formulations mentioned constitute an example given solely by way of practical demonstration of the invention, it being possible for the composition to vary within the limits defined in the attached claims without thereby departing  
25 from the scope of the underlying concept of this invention.

Claims

1. Preparation for treating the skin, including, in combination:
  - collagen;
  - 5 - elastin;
  - at least one acid chosen from deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) or a salt thereof;
  - a vehicle and/or an excipient.
2. Preparation according to Claim 1, additionally including a local vasodilatory substance.
- 10 3. Preparation according to Claim 1, additionally including at least one enzyme chosen from the group including: pepsin, pyridoxine, biotin.
4. Preparation according to Claim 1, 2 or 3, additionally including at least one amino acid chosen from the group including: glycine, proline, hydroxyproline, lysine, tyrosine, isodesmosine.
- 15 5. Preparation according to one or more of the preceding claims, additionally including Vitamin C.
- 20 6. Preparation according to one or more of the preceding claims, additionally including keratin.
7. Preparation according to claim 2, in which the said vasodilatory substance is procaine hydrochloride.
8. Preparation according to Claim 2, including in combination, expressed in parts by weight:
  - Hydrolysed collagen: 3-10 parts
  - Hydrolysed elastin: 1-4 parts
  - Procaine hydrochloride (vasodilator) 1-3 parts
  - Sodium deoxyribonucleate or equivalent 3-10 parts
  - 30 Sodium ribonucleate or equivalent 3-10 parts.
9. Preparation according to Claim 8, including in combination, expressed in parts by weight:
  - Hydrolysed collagen: 4-9 parts
  - Hydrolysed elastin: 2-4 parts
  - 35 Procaine hydrochloride 1.5-2.5 parts
  - Sodium deoxyribonucleate or equivalent 4-8 parts
  - Sodium ribonucleate or equivalent 4-8 parts.
10. Preparation according to Claim 2, including in

combination, expressed in parts by weight:

Hydrolysed collagen: 3-10 parts

Hydrolysed elastin: 1-4 parts

Procaine hydrochloride 1-3 parts

5 Sodium deoxyribonucleate or equivalent 5-20 parts.

11. Preparation according to Claim 2, including in combination, expressed in parts by weight:

Hydrolysed collagen: 3-10 parts

Hydrolysed elastin: 1-4 parts

10 Procaine hydrochloride 1-3 parts

Sodium ribonucleate or equivalent 5-20 parts.

12. Preparation according to one or more of the preceding claims, including an excipient and a vehicle for topical application.

15 13. Preparation according to one or more of Claims 1 to 11, including a physiological solution for intradermal or subcutaneous application as vehicle.

14. Preparation according to one or more of Claims 1 to 11, including, per 10 grams of product:

20 Hydrolysed collagen: 30-100 mg

Hydrolysed elastin: 10-40 mg

Procaine hydrochloride: 10-30 mg

Sodium deoxyribonucleate or equivalent 30-90 mg

Sodium ribonucleate or equivalent 30-90 mg

25 Glycine 25-75 mg

Proline 100-300 mg

Hydroxyproline 25-75 mg

Lysine 75-225 mg

Tyrosine 5-15 mg

30 Isodesmosine 20-60 mg

Pepsin 375-1125 mg

Pyridoxine 250-750 mg

Biotin 25-75 mg

Vitamin C 250-750 mg

35 Physiological solution qs 10 grams

15. Preparation according to Claim 14, additionally including from 15 to 45 mg of hydrolysed keratin per 10 g of product.

16. Preparation according to Claim 14, including, per 10 grams of product:
- |    |  |             |
|----|--|-------------|
|    | Hydrolysed collagen:                   | 45-85 mg    |
|    | Hydrolysed elastin:                    | 15-35 mg    |
| 5  | Procaine hydrochloride:                | 15-25 mg    |
|    | Sodium deoxyribonucleate or equivalent | 40-80 mg    |
|    | Sodium ribonucleate or equivalent      | 40-80 mg    |
|    | Glycine                                | 35-65 mg    |
|    | Proline                                | 140-260 mg  |
| 10 | Hydroxyproline                         | 35-65 mg    |
|    | Lysine                                 | 100-200 mg  |
|    | Tyrosine                               | 7-13 mg     |
|    | Isodesmosine                           | 30-50 mg    |
|    | Pepsin                                 | 525-975 mg  |
| 15 | Pyridoxine                             | 350-650 mg  |
|    | Biotin                                 | 35-65 mg    |
|    | Vitamin C                              | 350-650 mg  |
|    | Hydrolysed keratin                     | 20-40 mg    |
|    | Physiological solution                 | qs 10 grams |
- 20 17. Preparation according to one or more of Claims 1 to 11, for topical use, including, per 10 grams of product:
- |    |  |             |
|----|--|-------------|
|    | Hydrolysed collagen:                   | 65-200 mg   |
|    | Hydrolysed elastin:                    | 25-75 mg    |
| 25 | Procaine hydrochloride:                | 20-60 mg    |
|    | Sodium deoxyribonucleate or equivalent | 60-180 mg   |
|    | Sodium ribonucleate or equivalent      | 60-180 mg   |
|    | Glycine                                | 50-150 mg   |
|    | Proline                                | 200-600 mg  |
| 30 | Hydroxyproline                         | 50-150 mg   |
|    | Lysine                                 | 150-450 mg  |
|    | Tyrosine                               | 10-30 mg    |
|    | Isodesmosine                           | 40-120 mg   |
|    | Pepsin                                 | 750-2250 mg |
| 35 | Pyridoxine                             | 500-1500 mg |
|    | Biotin                                 | 50-150 mg   |
|    | Vitamin C                              | 500-1500 mg |
|    | Vehicle                                | 100-300 mg  |



Deionized water qs 10 grams

18. Preparation according to Claim 17, including, per 10 grams of product:

	Hydrolysed collagen:	90-170 mg
5	Hydrolysed elastin:	30-70 mg
	Procaine hydrochloride:	30-50 mg
	Sodium deoxyribonucleate or equivalent	80-160 mg
	Sodium ribonucleate or equivalent	80-160 mg
	Glycine	70-130 mg
10	Proline	280-520 mg
	Hydroxyproline	70-130 mg
	Lysine	200-400 mg
	Tyrosine	15-25 mg
	Isodesmosine	60-150 mg
15	Pepsin	1050-1950 mg
	Pyridoxine	700-1300 mg
	Biotin	70-130 mg
	Vitamin C	700-1300 mg
	Vehicle	150-230 mg
20	Deionized water	qs 10 grams

19. Preparation according to Claim 17 or 18, additionally including, per 10 grams of product, from 0 to 10 mg and preferably from 3 to 6 mg of sodium hydroxide.

25 20. Preparation according to one or more of Claims 17 to 19, in which the said vehicle includes hydrogenated polyoxyethylenated castor oil.

21. Preparation according to one or more of Claims 17 to 20, additionally including, per 10 grams of  
30 product, from 50 to 200 mg and preferably from 80 to 140 mg of an excipient which is physiologically compatible with topical application.

22. Preparation according to Claim 21, in which the said excipient is an acrylic acid polymer.

35 23. Preparation according to one or more of Claims 16 to 18, additionally including, per ten grams of product, from 30 to 90 mg and preferably from 40 to 70 mg of hydrolysed keratin.

24. Cosmetic treatment of the skin, including the application of a preparation according to one or more of Claims 1 to 24.

25. Treatment according to Claim 24, in which the said preparation is applied by subcutaneous, intradermal or mesodermal infiltration into the area to be treated.

26. Treatment according to Claim 24, in which the said preparation is applied topically.

27. Treatment according to Claim 26, in which the said preparation is applied in the form of a cream or an ointment.

28. Treatment according to Claim 26, in which the said preparation is applied in the form of an aqueous suspension by rubbing it in.

29. Use of a combination of the following substances:

- collagen;
- elastin;
- at least one acid chosen from deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), or a salt thereof;
- a vehicle and/or an excipient,

for the preparation of a medical product for the therapeutic treatment of skin pathologies.

30. Use of a combination of the following substances:

- collagen;
- elastin;
- at least one acid chosen from deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), or a salt thereof;

- a vehicle and/or an excipient,  
for the preparation of a product for cosmetic use in the treatment of unaesthetic skin conditions.

31. Use according to Claim 29 or 30, including the use of a local vasodilatory substance.

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K7/48 A61K7/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 592 790 A (VILLANO GUY) 17 July 1987  see the whole document	1,12,13, 24-30
A	--- CHEMICAL ABSTRACTS, vol. 121, no. 8, 22 August 1994 Columbus, Ohio, US; abstract no. 91353, SUZUKI, TADASHI ET AL: "cosmetics for rough skin" XP002030251 see abstract & JP 06 128 138 A (KYOWA HAKKO KOGYO KK, JAPAN; KOSEI KK) --- -/--	1-31

☒ Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search

25 April 1997

Date of mailing of the international search report

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## INTERNATIONAL SEARCH REPORT

International Application No.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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